Critical Analysis of Cerebrovascular Autoregulation During Repeated Head-Up Tilt

Richard L. Hughson, PhD; Michael R. Edwards, MSc; Deborah D. O'Leary, MSc; J. Kevin Shoemaker, PhD

Background and Purpose—Cerebrovascular autoregulation has been described with a phase lead of cerebral blood flow preceding changes in cerebral perfusion pressure (CPP), but there has been less focus on the effect of CPP on cerebral vascular resistance. We investigated these relations during spontaneous fluctuations (control) and repeated head-up tilt.

Methods—Eight healthy adults were studied in supine rest and repeated tilt with 10-second supine, 10 seconds at 45° head-up tilt for a total of 12 cycles. Cerebral blood flow was estimated from mean flow velocity (MFV) by transcranial Doppler ultrasound, CPP was estimated from corrected finger pressure (CPP\textsubscript{F}), and cerebrovascular resistance index (CVR\textsubscript{i}) was calculated in the supine position from CPP\textsubscript{F}/MFV. Gain and phase relations were assessed by cross-spectral analysis.

Results—In the supine position, MFV preceded CPP\textsubscript{F}, but changes in CVR\textsubscript{i} followed CPP\textsubscript{F}. Gain and phase relations for CPP\textsubscript{F} as input and MFV as output were similar in supine and repeated tilt experiments. Thus, changes in cerebrovascular resistance must have had a similar pattern in the supine and tilt experiments.

Conclusions—Cerebrovascular autoregulation is achieved by changes in resistance in response to modulations in perfusion pressure whether spontaneous or induced by repeated tilt. The phase lead of MFV before CPP\textsubscript{F} is a mathematical and physiological consequence of the relation the input variable (CPP\textsubscript{F}) and the manipulated variable (cerebrovascular resistance) that should not be taken as an indication of independent control of cerebral blood flow. (Stroke. 2001;32:2403-2408.)

Key Words: autoregulation \(\blacktriangleright\) cerebral blood flow \(\blacktriangleright\) ultrasonography, Doppler transcranial

Cerebral blood flow (CBF) is a tightly regulated variable under the control of a complex system, which, for constant arterial P\textsubscript{CO\textsubscript{2}}, attempts to rapidly counter changes in cerebral perfusion pressure (CPP) to maintain CBF near the desired set point. Cerebral autoregulation is normally operative across a range of CPP from 50 to 170 mm Hg.\textsuperscript{1} Since the work of Aaslid et al\textsuperscript{2} in 1989, there has been considerable interest in the dynamic nature of cerebral autoregulation. Aaslid and colleagues\textsuperscript{2,\textsuperscript{4}} used a sudden release of occlusion cuffs placed about the upper thigh to achieve a “step” decrease in CPP and observed the rapidity of the change in cerebral vascular resistance (CVR). They were able to categorize different rates of response and quantify impaired autoregulation.

Dynamic autoregulation has also been studied by Birch et al\textsuperscript{3} with repeated squatting exercise to manipulate arterial pressure. In a similar manner, Diehl et al\textsuperscript{6} had their subjects perform repeated slow, deep breathing to achieve oscillations in arterial blood pressure while monitoring CBF. Both of these research groups as well as investigators who monitored spontaneous oscillations in CPP\textsuperscript{7,\textsuperscript{9}} focused on the phase lead of CBF preceding CPP as a means of quantifying cerebral autoregulation. Yet, when CPP is changed as a step function as with the release of leg cuffs, CBF lags, it does not lead the change in CPP.\textsuperscript{2} There has not been a clear description of why CBF should lead CPP during spontaneous oscillations in CPP or during the squatting or deep breathing experiments. Recently, Cencetti et al\textsuperscript{10} argued that the phase lead of CBF before CPP indicated that autonomic modulation of the cerebrovasculature was able to “predominate over local autoregulatory mechanisms.” These discrepant observations suggest that further investigation is required to explore the phase relations between input and output responses of cerebrovascular control.

In this study, we explored the phase relations between the 3 components of Ohm’s law applied to the circulation; that is, pressure, flow, and resistance. Cerebral perfusion pressure was estimated by the Finapres device (CPP\textsubscript{F}); mean flow velocity (MFV) in the middle cerebral artery was measured by Doppler ultrasound; and, in the supine position, cerebral vascular resistance index (CVR\textsubscript{i}) was calculated from CPP\textsubscript{F}/MFV. In addition, we tested the phase relations between CPP\textsubscript{F}...
and MFV during repeated tilt that induced large, rapid variations in CPPF. We hypothesized that the changes in CPPF are followed by changes in CVRi that function to restore MFV toward normal levels. We show that the apparent phase lead of MFV before CPPF is a mathematical consequence of the normal lag of CVRi after changes in CPPF.

**Subjects and Methods**

Eight healthy young subjects (6 men and 2 women, 25 ± 5.9 years of age, mean ± SD) volunteered for this study after receiving complete verbal and written details. The Office of Research Ethics at the University of Waterloo approved the research protocol.

Subjects were allowed to rest quietly in the supine position after instrumentation had been completed. Data were collected in the supine position before being alternately tilted to 45° for 10 seconds and returned to the supine position for 10 seconds for a total of 12 cycles in 4 minutes. Tilting was accomplished on a manually operated tilt table in <2 seconds.

MFV was determined by Doppler ultrasound (Transpect TCD, Medasonics) from the right middle cerebral artery (MCA) through the temporal window. Arterial blood pressure was estimated continuously by a servo-controlled photoplethysmograph (Finapres, Ohmeda) placed on the middle finger of the right hand. The finger cuff pressure is widely used as an estimate of arterial pressure, although absolute values sometimes differ. Given this limitation, we chose to refer to gravity-corrected finger arterial pressure as CPPF to provide an estimate of CPP. Heart rate was recorded by ECG. End-tidal PCO2 was monitored from a nasal cannula with an infrared CO2 analyzer (Pilot, Colin). Average values of end-tidal PCO2 were obtained in the supine and tilted positions.

The finger cuff of the blood pressure monitor was positioned to rest comfortably on the subject's chest and then held in position by a sling connected to the tilt table. To correct blood pressure from this device to heart level and also to brain level, 2 pressure transducers (Transstar, Furon) were connected to amplifier circuits (Pilot, Colin). Both of these transducers were placed on the lateral midline to coincide with the aortic valve so that when subjects were tilted there was no change in the reference point with respect to the heart. One water-filled catheter tip was placed at the level of the finger cuff to correct finger pressure to arterial pressure; the other catheter tip was positioned at the cerebral Doppler probe so that arterial pressure could be adjusted to CPPF. The transducers were calibrated against a column of water, and values were converted to millimeters of mercury.

**Data Analysis and Statistics**

Data were recorded on digital format tape (TEAC), then transferred for analysis by a computer-based system to yield a data set sampled at 100 Hz. MFV was determined from the outer envelope of the fast Fourier transformed cerebral Doppler signal. Beat-by-beat values were obtained for mean arterial pressure (MAP) and CPPF by averaging the corrected pressure waveforms over each cardiac cycle. CVRi was calculated as CPPF/MFV without reference to intracranial pressure, as discussed later. Autospectra of MFV, CPPF, and CVRi were calculated within 3 distinct frequency regions (very low frequency [VLF] from 0 to 0.07 Hz, low frequency [LF] from 0.07 to 0.2 Hz, and high frequency [HF] from 0.2 to 0.3 Hz) to correspond to those used previously by Zhang et al. Cross-spectral power, transfer function gain, phase, and coherence were determined within the same frequency regions for the relations between CPPF and MFV. Gain and phase relations were obtained only from those regions of the spectra where coherence was ≥0.5. This critical value is commonly used because it represents a value well above that required (0.32) to indicate a squared coherence that was significantly different from zero (P < 0.01).

Data are expressed as mean ± SD. The observed responses during baseline and tilt periods for autospectral power as well as gain and phase relations of the cross-spectra were compared by 1-way, repeated-measures ANOVA.

**Results**

A sample of the continuous data record is shown in Figure 1. This figure reveals the spontaneous variation in CPPF, MFV, and CVRi that occurred in the baseline collection and during tilt. The magnitude of these variations and the increase with repeated tilt can be appreciated from the spectral power (Table 1). To provide a visual analysis of the spontaneous phase relation, a solid vertical line has been added to Figure 1 at the peak of the CPPF oscillation that occurred just before the first tilt. With reference to this line, it is clear that the peak of the oscillation in MFV preceded the peak in CPPF and that the peak change in CVRi followed. That this was the common observation is confirmed from the cross-spectral analysis for

<table>
<thead>
<tr>
<th>TABLE 1. Autospectral Power During Baseline and Repeated Tilt Periods</th>
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<tr>
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<tr>
<td>MFV, cm/s²</td>
</tr>
<tr>
<td>VLF</td>
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<tr>
<td>LF</td>
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<tr>
<td>HF</td>
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<tr>
<td>CPPF, mm Hg²</td>
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<td>VLF</td>
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<td>LF</td>
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<tr>
<td>HF</td>
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<tr>
<td>CPPF/MFV† (mm Hg · cm² · s⁻²)</td>
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<tr>
<td>VLF</td>
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<tr>
<td>LF</td>
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<tr>
<td>HF</td>
</tr>
</tbody>
</table>

*Values are mean±SD for 8 subjects. VLF, LF, HF frequency regions as described in Materials and Methods.

†Significantly different from baseline, P < 0.05.
TABLE 2. Transfer Function Gain and Phase Relations During Baseline and Repeated Tilt Protocols

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Baseline</th>
<th>Repeated Tilt</th>
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<tbody>
<tr>
<td>CPP(_i)→MFV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gain, cm·s·mm Hg(^{-1})</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VLF</td>
<td>4</td>
<td>0.40±0.28</td>
<td>0.33±0.12</td>
</tr>
<tr>
<td>LF</td>
<td>7</td>
<td>0.78±0.34</td>
<td>0.43±0.10</td>
</tr>
<tr>
<td>HF</td>
<td>8</td>
<td>0.93±0.31</td>
<td>0.52±0.17*</td>
</tr>
<tr>
<td>Phase, degrees</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VLF</td>
<td>4</td>
<td>30.9±40.6</td>
<td>55.9±25.0</td>
</tr>
<tr>
<td>LF</td>
<td>7</td>
<td>42.0±20.7</td>
<td>38.3±19.0</td>
</tr>
<tr>
<td>HF</td>
<td>8</td>
<td>8.2±62.8</td>
<td>-9.1±1.2</td>
</tr>
<tr>
<td>CPP(_i)=CPP(_c)/MFV†</td>
<td></td>
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<tr>
<td>Gain, units/mm Hg</td>
<td></td>
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<tr>
<td>VLF</td>
<td>7</td>
<td>0.019±0.005</td>
<td>0.016±0.003</td>
</tr>
<tr>
<td>LF</td>
<td>8</td>
<td>0.016±0.006</td>
<td>0.014±0.003</td>
</tr>
<tr>
<td>HF</td>
<td>6</td>
<td>0.015±0.010</td>
<td>0.012±0.005</td>
</tr>
<tr>
<td>Phase, degrees</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VLF</td>
<td>7</td>
<td>-16.8±24.6</td>
<td>-14.5±13.5</td>
</tr>
<tr>
<td>LF</td>
<td>8</td>
<td>-28.8±59.7</td>
<td>3.1±51.7*</td>
</tr>
<tr>
<td>HF</td>
<td>6</td>
<td>-53.1±26.9</td>
<td>-13.3±13.7</td>
</tr>
</tbody>
</table>

Values are mean±SD. Number of subjects (n) was determined by coherence ≥0.5 in baseline. When there was not sufficient coherence in baseline, only those same subjects were included under repeated tilt.

*Significantly different from baseline by repeated-measures ANOVA, P<0.05.
†For baseline, CPP\(_c\)/MFV is equivalent to CVR\(_i\) as defined in text, (units=mm Hg·cm\(^{-1}\)·s\(^{-1}\)).

The baseline data in which across all frequency ranges there was a phase lead for MFV ahead of CPP\(_i\), whereas CVR\(_i\) lagged CPP\(_i\) (Table 2).

The interesting interactions between CPP\(_c\), MFV, and CPP\(_c\)/MFV (the latter a reflection of vascular resistance) became apparent with the repeated tilt protocol (Figure 1). Because changes in vascular resistance must always lag the change in CPP\(_c\) with tilt up or tilt down, the immediate change in CPP\(_c\) caused rapid changes in MFV. The subsequent adjustment of vascular resistance caused MFV to be normalized; however, the timing was such that MFV reached its peak early in each 10-second period of postural change, whereas CPP\(_c\) was relatively constant. The timing of the peak of MFV compared with the midpoint in the oscillation of CPP\(_c\) provided the appearance of MFV “leading” CPP\(_c\). Cross-spectral analysis confirmed this phase lead of MFV before CPP\(_c\) during the repeated tilt protocol (Table 2).

End-tidal PCO\(_2\) was 39.5±2.8 mm Hg during the supine resting baseline period and it returned to approximately this value with each tilt down to the supine position. However, during all head-up tilts, end-tidal PCO\(_2\) decreased to 35.5±4.6 mm Hg (P<0.05).

During the supine baseline period, cross-spectral analysis revealed the anticipated phase lead of MFV before CPP\(_c\), especially in the LF region (Table 2). The differing sample size presented in the table indicates that not all subjects had coherence >0.5 in the selected frequency ranges. During the repeated tilt manipulations, the phase relations between MFV and CPP\(_c\) were not different from the baseline. The gain of the relation between CPP\(_c\)→MFV was similar during the baseline and repeated tilts in the VLF and LF regions but was reduced during repeated tilt in the HF region.

In the supine baseline period we were able to evaluate the relation between CPP\(_c\)→CVR\(_i\). Changes in CVR\(_i\) lagged changes in CPP\(_c\) across all frequency regions in the supine position (Table 2). The slight increase in phase lag from VLF to LF to HF is consistent with a time lag of ≈1 second. With repeated tilt, the assumption of constant intracranial or venous pressure is violated so that CPP\(_c\)/MFV does not provide the same information about CVR\(_i\) as in the supine position. However, it is evident that CPP\(_c\)/MFV during rapid tilt had almost identical values for gain and differed in phase relation only in the LF band when compared with the CVR\(_i\) during supine baseline.

Discussion

These data support our hypothesis that a cyclic change in CPP, whether spontaneous or induced by rapid tilt, would be followed by an appropriate change in cerebrovascular resistance in an attempt to maintain MFV near the desired set point value. Further, the supine baseline data clearly show how the interaction between CPP and CVR\(_i\) result in an apparent phase lead of MFV before CPP. As previously suggested by Aaslid and colleagues2–4 on the basis of their leg cuff deflation experiments, CPP and CVR\(_i\) are the appropriate variables to investigate to understand the control of CBF. We have shown that the apparent phase “lead” of MFV to CPP is merely a mathematical consequence of the relation between the physiological response of CVR\(_i\) to CPP. This latter observation is in stark contrast to the speculation of some researchers that the phase lead of MFV to CPP indicates autonomic control over cerebral blood vessels that precedes and then establishes the vascular tone in the rest of the body.10

Methodological Considerations

We used transcranial Doppler ultrasound to continuously monitor changes in CBF. This technique has been widely used under the assumption that the cross-sectional area of the middle cerebral artery does not change.2,5,8,12,13 Recent measurements of the MCA during application of lower body negative pressure in both hypocapnia and hypercapnia confirmed that this vessel is quite stable across a marked range of CBF.14

Vascular resistance is defined as the ratio of the pressure drop to flow across the vascular bed. The three components, pressure drop, flow, and resistance, are not and cannot be independent variables.15 In the case of cerebrovascular resistance, calculation is complicated by the difficulty in directly determining the pressure drop due to unknown values of intracranial pressure and venous pressure. We have used the ratio CPP\(_c\)/MFV as an estimate of CVR\(_i\) during supine studies. This estimate will provide a reliable indicator of changes in cerebrovascular resistance as long as venous pressure does not change appreciably and as long as the components (CPP\(_c\) and MFV) are measured without error. The stable Doppler probe will minimize any random error in measurement of MFV, and the Finapres, although often
subject to systematic error, is not subject to random error. Thus, CVR will reflect changes in CVR in the supine position.

During the repeated tilt experiments, we reported the CPP/MFV as a reflection of changes in CVR. Under the tilt protocol, intracranial and venous pressure almost certainly varied, invalidating the ratio CPP/MFV as an index of CVR across body positions. CPP/MFV responded in the manner that we anticipated during the up and down tilts. It is interesting that the magnitude and phase relations for CPP/MFV during repeated tilt were similar to those of CVR in supine baseline. This suggests to us that the CPP/MFV provided a useful indicator of changes in cerebrovascular dynamics. In our population of healthy young volunteers it was impossible to obtain direct measurements of intracranial pressure in an attempt to improve our understanding of cerebrovascular resistance. It is not clear how much intracranial pressure changes with head-up tilt, especially with our repeated tilt protocol, and recent direct measurements suggest that intracranial pressure might change independent of changes in cerebrovascular tone.

Alternative methods to interpret changes in CVR such as estimation of critical closing pressure (CCP) or resistance area product derived with respect to CCP (RAP) have been used, although questions remain about this approach. CCP is obtained by extrapolation to the pressure axis of the linear regression between CPP and MFV over individual cardiac cycles. RAP is the inverse of the slope of the linear regression. For the subject shown in Figure 1, estimated CCP was 12.9 mm Hg in supine and −6.1 mm Hg during tilt. The corresponding RAP values were 0.95 and 0.84 mm Hg · s⁻¹ · cm⁻¹. These alternative indirect indexes are consistent with our data suggesting lower vascular resistance during the tilt.

**Baseline Cerebrovascular Dynamics**

Spectral analysis of the modulations in CPP and MFV yielded transfer gain and phase relations between these variables that were similar to those reported in previous investigations. We selected our frequency ranges to permit direct comparison to the results for spontaneous fluctuations in CPP reported by Zhang et al. In the VLF region of the spectrum (0.0 to 0.07 Hz), the low coherence between CPP and MFV suggests that autoregulation is effective in this region. At relatively higher frequencies, greater coherence indicated a link between changes in MFV and CPP. In the frequency range of 0.07 to 0.20 Hz, the gain of MFV relative to CPP (Table 2) was slightly less than reported by Zhang et al. whereas the phase lead of 42 ± 7° for MFV before CPP was within the range for spontaneous fluctuations in CPP and for repeated squatting exercise. As the frequency increased above 0.20 Hz, the phase difference between signals was reduced to a value not different from zero, indicating that oscillations in CPP were directly transmitted to MFV.

Unlike the previous studies, we determined the coherence, gain, and phase relations between CPP and CVR. There was significant coherence between CPP and CVR in at least 6 of 8 subjects across all frequency intervals (Table 2). The phase was consistently negative, indicating a phase lag of CVR behind CPP. The gain values were almost identical across all frequency intervals. The response of CVR after a change in CPP is the expected response of a closed-loop negative feedback system. That is, CVR is the manipulated variable that attempts to modulate the cerebral vasculature to allow CBF to be maintained near the set point by autoregulatory mechanisms.

**Response to Tilt**

During tilt, the autospectral power for each variable increased, especially near the frequency of the tilt, as the result of the introduction of large variations in CPP. The reduction in CPP with the first head-up tilt differs somewhat from the decrease in CPP observed with the rapid deflation of a leg cuff. CPP recovered to baseline after cuff release but not after head-up tilt. With cuff release, there was probably no effect on intracranial pressure (or CCP), whereas in the current study, CCP decreased with tilt. The models are not identical, but the effect on CVR was directionally similar. With tilt, MFV decreased rapidly at first, then returned to values that were slightly below the pretilt baseline (Figure 1). The dynamic autoregulatory index indicated that the "normal" subject response required ~5 seconds for the MFV to recover to ~98% of the prestep decrease in CPP. This is consistent with the observation in Figure 1. With both the leg cuff release and head-up tilt, MFV followed the change in CPP; it did not precede it as suggested from cross-spectral analysis. MFV appears to precede CPP during repeated squatting, deep breathing, and even the simple analysis shown by the solid vertical line drawn through the spontaneous variations in CPP in Figure 1. However, we argue that the phase relation between CPP and MFV does not provide an accurate indication of vascular responses to CPP changes.

With the first tilt back to the supine position, we were able to study the response to a rapid increase in perfusion pressure. The tilt back to supine caused CPP to reach a relatively stable value similar to that observed in the supine baseline. MFV increased rapidly with the tilt down, then returned toward the baseline value during the latter part of this 10-second period in the supine position. That is, MFV showed rapid changes on moving to head up or supine positions that were initiated by changes in perfusion pressure but must have been compensated through adjustments in CVR. The consequence of this sequence of events was that cross-spectral analysis suggested that changes in MFV preceded CPP, but in reality it was only the mid-point of the peak change in MFV that occurred before the mid-point of the change in CPP.
with the results from the squatting exercise. By comparing responses for CVRi during baseline with the CPP/MFV during repeated tilt, we found that there, too, the gain and phase relations were similar during baseline and repeated tilt protocols. Visual analysis of Figure 1 indicates how the repeated tilt protocol has been able to provide valuable insight because it can be appreciated that changes in CPP, whether spontaneous or induced by repeated tilt, caused a change in the indicators of cerebrovascular resistance, which then in turn modified MFV.

Interaction With PCO₂
With the repeated tilting, there was a consistent decrease in end-tidal Pco₂ in the upright position. This decrease in Pco₂ is a common finding that might be a consequence of maintained alveolar ventilation with reduced CO₂ return to the lungs as venous return decreases with tilt. It is well established that reductions in arterial Pco₂ will cause an increase in CVRi. Thus, regulation of CBF on going to the head-up position is the sum of the complex interactions of altered pressure gradient, dilation to counter the reduction in CPP, and constriction resulting from lower arterial Pco₂. Indeed, Figure 1 shows the clear reduction in MFV in the upright position compared with the supine baseline or the supine position between tilts. This suggests that in addition to changes in CPP, the change in arterial Pco₂ did play an important role in establishing CBF.

Interpreting Cerebrovascular Dynamics
In a recent article, Cencetti et al concluded that the phase lead of MFV before CPP was an indication of neural control of the cerebrovascular system. They based their conclusion on spectral analysis of various signals from the cardiovascular system that showed oscillations in MFV preceded all of these other variables. We present an argument to demonstrate that the response of MFV is simply a consequence of the nonlinearity in the calculation of CVR. Specifically, it appears that when MFV and CPP are assumed to bear a linear relation, CVR responds more slowly to an increase in CPP than it does to a decrease (Figure 2). If these assumptions prove to be true, the nonlinear response of CVR might be a very valuable physiological response to prevent fainting, because it would allow for rapid adjustments in CBF on moving from a supine to an upright posture. Panerai et al recently suggested application of a nonlinear model to fit MFV and CPP. Further research is required to determine where nonlinear models might improve our interpretation of the results.

Conclusions
The repeated tilt model demonstrated that the cerebrovascular system behaved as a closed-loop negative feedback system. The primary regulated variable, CBF, was kept within a relatively narrow range by rapid adaptations of the manipulated variable, CVR, in response to changes in CPP. The important concept advanced by this study was that research should focus on the control of CVR in response to changes in CPP. Unlike previous research that indicated the importance of the “phase lead” of MFV before CPP, we showed that this phase lead is simply a consequence of the interaction of the mechanisms responsible for control of CBF. The “phase lead” is a mathematical consequence of the phase lag of CVR. The response of CVR occurring with spontaneous fluctuations in

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*Figure 2. Schematic of interrelations between CPP, MFV, and CVR during baseline and repeated tilt.*

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*Model of Cerebrovascular Interactions*
CPP, repeated tilt, or leg cuff deflation is a better indication of the efficiency of cerebrovascular autoregulation.

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